Genomic architecture presages genomic instability: study

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When cells divide normally, DNA gets copied perfectly and distributed among the daughter cells with an even hand. Occasionally though, DNA breaks during division and is rearranged, resulting in duplications or deletions of important parts of the blueprint.

Now researchers at Baylor College of Medicine who study families with such genomic disorders have found a shared, yet unusual, architecture resulting from this jumble that is associated with very severe forms of disease. They also identified the genomic elements that produce such architecture, a finding that will help predict other unstable regions in the human genome.

The unusual architecture left a footprint, and a search for similar footprints in other regions of the genome may identify regions that underwent the same alteration during the evolutionary past. This event might occur more often than previously expected. A report on their work appears online in the current issue of *Nature Genetics*.

The rearrangement structure – triplicated genetic material inverted and embedded within duplications of genetic material – appeared in 20 percent of patients who had been diagnosed with MECP2 duplication syndrome, said first author Dr. Claudia Carvalho, a postdoctoral associate in the laboratory of Dr. James Lupski, vice chair of the department of molecular and human genetics at BCM and corresponding author of the report.

A mutation in MECP2 was first identified in association with Rett syndrome by the laboratory of Dr. Huda Zoghbi at BCM. In Rett syndrome, the protein associated with the gene has minimal or no activity and the disorder mainly affects girls. Later studies showed that too much MeCP2 protein because of increased MECP2 gene dosage could cause another serious disorder – this time in boys and called MECP2 duplication syndrome.

In this new discovery, patients with the unusual complex triplication – called in shorthand, DUP (duplication)-TRP (triplication)/INV (inverted)-DUP – had a more severe constellation of symptoms associated with the genomic disorder. The patients required oxygen or a ventilator and had hearing loss, heart defects and difficulty swallowing that necessitated a feeding tube. In most patients with the syndrome, developmental delays in motor skills, limited or absent speech, autistic behavior, intellectual disability and recurrent infections are also typical symptoms.

"Dr. Melissa Ramocki (another of the paper's first authors and an assistant professor of pediatrics – neurology at BCM) started to be able to predict which patients would have the DUP-TRP/INV-DUP," said Lupski. This means that the increased amount of genetic material increased the dosage of MeCP2 protein and made the disorder worse.

Carvalho proposes that the rearrangement may have occurred during the sperm cell generation. During meiosis (sexual cell division), a cell divides and produces four haploid cells containing one copy of each chromosome. The resulting chromosome set in each gamete (sperm or egg) cell is a unique mixture of paternal and maternal DNA, ensuring that offspring are genetically distinct from either parent. The process involves copying DNA and producing new strands for which special cellular machinery exists.

Sometimes, this process goes wrong. At one point, a piece of DNA replication machinery called the replication fork may collapse, forcing the cell to trigger its repair process. When the cell tries to make a new fork, the DNA can line up improperly and pair with a piece of seemingly compatible DNA oriented in the opposite direction. These elements called "inverted repeats" are ubiquitous in the human genome. This first event causes replication of the DNA in the wrong direction – opposite to the way that it was going when the fork collapsed, which will lead to a segmental inverted duplication. A second event, believed to be obligatory to the viability of the cell, will bring the replication fork back into the correct direction and resume the replication process. This second event may now produce a triplication if the new replication fork is re-established within the region that was just copied twice.

This jumble of machinery, mismatched DNA ends and aberrant reproduction of the genetic material can cause the strange complex triplication rearrangement that results in disease, and it appears to occur in more than just MECP2 duplication syndrome.

Studying patients with another genomic disorder associated with the PLP1 gene, the researchers were able to find the same unusual genomic architecture (The PLP1 gene is associated with Pelizaeus-Merzbacher Disease, Spastic Paraplegia 2). In each case, inverted repeats of genomic DNA sequence appear to help mediate the complex inverted triplication.

"These inversions are important," said Carvalho. "There is no easy way to assay them, and we don't know how common they are in the genome."

"It may be possible that there are a lot of disease genes there and we don't see them," said Lupski. "The same mechanism that causes disease might also be involved in evolutionary change. In fact, this mechanism may have created new genes that might have made us more fit for our environment."

Dr. Philip J. Hastings, professor of molecular and human genetics at BCM who has studied mutational events resulting in rearrangements of different genomes for many decades, helped work out how the rearrangements might happen and is an author on the report as well.

Provided by Baylor College of Medicine

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